Remarks

The Office Action dated March 18, 2002 has been carefully reviewed. In view of the following remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims. Applicant respectfully submits that no prohibited new matter has been introduced by the amendments. While written description support for the amendments can be found throughout the specification and original claims, specific support for the amendments to the specification can be found in original claims 1, 5, 9, 10, 12 and 13 while specific support for the claim amendments can be found in original claim 10 and in the specification on page 8, lines 16-17.

Summary of the Office Action

1. The request for continued examination under was granted and the finality of the previous Office Action was withdrawn pursuant to 37 C.F.R. 1.114.

2. The art rejections of record were withdrawn in view of Applicant's claim amendments and remarks in the amendment dated May 8, 2001.

3. The specification was objected to as failing to provide proper antecedent basis for the claimed subject matter under 37 C.F.R. 1.75(d)(1).

4. Claims 34-40 and 42-46 were rejected under 35 U.S.C. 112 (first paragraph) for containing subject matter which was not described in the specification in a manner such as to reasonably convey to the skilled artisan that the inventors, at the time the application was filed, had possession of the claimed invention.

Rejections under 37 C.F.R. 1.75(d)(1)

The specification was objected to as purportedly failing to provide proper antecedent basis for the claimed subject matter under 37 C.F.R. 1.75(d)(1). Applicant appreciates the Examiner's comments in the telephone discussion with Applicant's agent on September 17, 2002. In view of the Examiner's comments, Applicant has amended the specification to incorporate the language found in the original claims into the specification. In light of these amendments to the specification, Applicant respectfully requests that the objection be withdrawn.

Rejections under 35 U.S.C. 112 (first paragraph)

Claims 34-40 and 42-46 were rejected under 35 U.S.C. 112 (first paragraph) for containing subject matter which was not described in the specification in a manner such as to reasonably convey to

the skilled artisan that the inventor, at the time the application was filed, had possession of the claimed invention. The Office Action requested that Applicant identify those sections of the specification where the basis for each claimed characteristic of the array, as well as basis for the subgenus of arrays having the claimed characteristics is disclosed.

The Office Action rejected claim 34, part (1) for use of the language "from about 20 to about 300 nucleotides" purportedly because the disclosure does not fairly provide basis or convey contemplation of this range. Applicant respectfully submits that the disclosure in the specification contemplates any modified oligonucleotide between the length of about 2 to about 300 nucleotides. See, for example, the specification at page 6, lines 19-20 ("the term "oligonucleotide" as used herein refers to a nucleic acid molecule comprising from about 2 to about 300 nucleotides"). Applicant brings to the Examiner's attention that a disclosure of range in the original specification is sufficient disclosure to meet the written description requirement for any claim limitation between the disclosed range (see *In re Wertheim*, 541 F.2d 257 and MPEP 2163.05). Applicant therefore submits that there is adequate written description in the specification to support a claim limitation of "about 20 to about 300 nucleotides" because these values fall within the range disclosed in the specification of 2 to 300 nucleotides.

The Office Action rejected claim 34, part (2) purportedly because the specification discloses only a list of internucleotide linkages with respect to end-blocked oligonucleotides and this feature is not a limitation of the claim. Applicant respectfully disagrees because the specification also discloses that the modified oligonucleotides can have the recited internucleotide linkages without any reference to being end-blocked on page 16, lines 13-25 ("oligonucleotides and/or polynucleotides of the invention may contain any modification that confers on the molecules greater binding with other nucleic acids, that increases the acid stability and/or increases the nuclease stability of the molecule. This includes oligonucleotides and/or polynucleotides completely derivatized by phosphorothioate linkages, 2'-O-methylphosphodiesters, 2'-O-alkyl, ... nucleotides in each oligonucleotide and/or polynucleotide may each contain the same modifications, may contain combinations of these modifications, or may combine these modifications with phosphodiester linkages").

The Office Action rejected claim 34, part (4) purportedly because the specification has no basis for a particular substitution at the 2' position of the ribose group, which distinguishes it from naturally occurring RNA or DNA. Applicant respectfully disagrees because this modification is disclosed in the specification on page 2, lines 24 to 26 ("modification at the 2' site of the sugar group"); on page 8, lines 6-7 ("in a preferred embodiment, the 2'-H or 2'-OH of the sugar group (for RNA and DNA, respectively)

may be altered to 2'-O-alkyl or 2'-O-alkyl-n(O-alkyl), which provides resistance to degradation") and in Figures 1-4 which display ribose structures with chemical modifications at the 2' position.

The Office Action rejected claim 34 purportedly because there is no basis in the specification for the limitation that the associated oligonucleotides of one area exhibit substantially the same melting temperature when bound to a target nucleic acid as oligonucleotides of another area of the array. Applicants respectfully disagree because the Office Action has not established a *prima facie* case as to why the specification lacks written description for the above claim limitation. The burden is on the Examiner to prove that the skilled artisan would not have recognized that the inventor was in possession of the claimed invention in view of the disclosure of the specification as filed (see *In re Wertheim*, 541 F.2d 257, 263 and MPEP 2163).

The Office Action indicates that "the specification ... does disclose arrays with oligonucleotides having the same Tm, however, this appears to be with respect to the entire array and just not selected portions of the array" (see Office Action at page 4, lines 7-9). The Office Action assumes that the specification discloses that all of the associated oligonucleotides of the array have the same melting temperature and does not identify why the skilled artisan at the time of application filing would not have recognized that the inventor was in possession of an array with associated oligonucleotides with different melting temperatures.

In addition, Applicant disagrees with the assumption that all of the associated oligonucleotides must have the same melting temperature because nowhere in the specification does it require that the associated oligonucleotides all have the same melting temperature. Rather, the specification is silent with regard to such limitations, indicating that the associated oligonucleotides can have the same or different melting temperatures when they are bound to a target nucleic acid. Applicants also bring to the Examiner's attention that without any specific attention to length and sequence of each modified oligonucleotide associated with the array, the melting temperature will vary across the array, the extent of variation in melting temperature being dependent upon the characteristics of the associated oligonucleotides on any particular array.

The Office Action rejected claims 35 and 36 purportedly because the specification has no basis for exonuclease resistance compared to oligonucleotides having the same number of residues. Applicant has amended these claims so that the end-blocked associated oligonucleotide has exonuclease resistance twice that of a naturally occurring nucleic acid having the same base sequence and length. Written

support for these claim amendments can be found in original claim 10 and in the as-filed specification on page 8, lines 16-17.

The Office Action rejected claim 34, part (5) purportedly because the specification has no basis for an array associated with modified oligonucleotides having a pH stability of at least one hour at 37°C at a pH in a range of about 0.5 to 6 with the combined limitations of parts (1), (2) and (4) of this claim. Applicant respectfully disagrees because the specification discloses that "the arrays of the present invention encompass associated oligonucleotides chemically modified to be acid stable from a pH of 0.01 to 7.0" (see page 11, lines 21-22). Chemically modified oligonucleotides of the invention are defined in the specification to include "oligonucleotides and/or polynucleotides with one or more chemical modifications at the molecular level of the natural molecular structures of all or any of the bases, sugar moieties, internucleotide phosphate linkages" (see page 6, lines 24-27). Thus, the term "chemically modified oligonucleotide" encompasses all the limitations set forth in parts (2) and (4) of claim 34 because it encompasses modified internucleotide linkages and modified sugar (ribose) moieties.

With regard to part (1) of claim 34, written description support can be found in the specification on page 6, lines 18-19 ("the term "oligonucleotide" as used herein refers to a nucleic acid molecule comprising from about 2 to about 300 nucleotides"). As chemically modified nucleotides are defined to be oligonucleotides, the term "chemically modified oligonucleotide" referred to above also encompasses the limitation of part (1) of claim 34.

In view of the claim amendments and aforementioned remarks, Applicant respectfully requests that the rejections under 35 U.S.C. 112 (first paragraph) be withdrawn.

Status of Co-Pending Applications

The Office Action requested the status of co-pending applications 09/223,498; 09/524,092 and 09/528,404. Application 09/223,498 has been abandoned. Application 09/524,092 is pending and contains claims directed to arrays with a plurality of modified oligonucleotides comprising at least one p-ethoxy internucleoside linkage or 3'-O-methyl substituent. Application 09/528,404 issued as U.S. Patent 6,440,723 on August 27, 2002 and is directed to arrays with a plurality of different modified oligonucleotides.

Conclusion

Applicant respectfully requests reconsideration of the subject application in view of the amendments to the claims and the above remarks. It is respectfully submitted that this application is now in condition for allowance. Should the Examiner believe it to be useful, an interview with the Examiner is respectfully requested in order to discuss the foregoing claims.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "version with markings to show changes made" as required. If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: **September 18, 2002**
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph beginning on page 2, line 22 through page 3, line 2 has been amended as follows:

In one embodiment, the modified associated oligonucleotides and/or polynucleotides of the invention provide additional binding affinity with respect to corresponding, unmodified oligonucleotides having the same sequence. The binding affinity is preferably increased by a modification at the 2' site of the sugar group, *e.g.*, a 2'-F or a 2'-OR modification such as 2'-O-methyl or 2'-O-methoxyethoxy. Alternatively or in combination, the binding affinity can be increased by modification in the 3' linkage group, *e.g.*, phosphoramidate linkages, or a modification replacing the oxygen with a carbon. In yet another embodiment, the modified associated oligonucleotides and/or polynucleotides are characterized by modification of at least 25% of the internucleoside linkages of the oligonucleotide and/or polynucleotide.

The paragraph beginning on page 3, line 3 has been amended as follows:

In another embodiment, the modified associated oligonucleotides and/or polynucleotides of the array exhibit substantial acid resistance, allowing the arrays to be treated with low pH solutions. This allows the array to be exposed to low pH in order to remove any bound nucleic acids that are not modified, *e.g.*, bound test nucleic acids. In yet another embodiment, the modified oligonucleotides and/or polynucleotides of the array have a pH stability of at least one hour at 37°C at a pH range of about 0.5 to about 10 including across the pH range of about 0.5 to 6.0.

The paragraph beginning on page 6, line 18 has been amended as follows:

The term "oligonucleotide" as used herein refers to a nucleic acid molecule comprising from about 2 to about 300 nucleotides. Oligonucleotides for use in the present invention are preferably from 80-200, more preferably from [~~100-150~~] about 100-200, and even more preferably from about 100-150 nucleotides in length.

The paragraph beginning on page 24, line 13 has been amended as follows:

--A single substrate supports more than about 10 different oligonucleotide and/or polynucleotide compositions and preferably more than about 100 different oligonucleotide and/or polynucleotide

compositions, although in some embodiments more than about 10^3, 10^4, 10^5, 10^6, 10^7, or 10^8 different compositions are provided on a substrate. In a preferred embodiment, the number of oligonucleotide compositions on an array ranges from about 2 to about 10^9. Of course, within a region of the substrate in which a modified oligonucleotide or polynucleotide is attached, it is preferred that the modified nucleotides be substantially pure. In preferred embodiments, regions of the substrate contain oligonucleotides or polynucleotides which are at least about 50%, preferably 80%, more preferably 90%, and even more preferably, 95% pure. Oligonucleotides or polynucleotides having several sequences can be intentionally provided within a single region so as to provide an initial screening for biological activity, after which materials within regions exhibiting significant binding are further evaluated. In a preferred embodiment, each region will contain a substantially pure modified oligonucleotide or polynucleotide composition having a single sequence.

In the Claims:

Claim 35 has been amended as follows:

35. (Twice Amended) The array of claim 34, wherein the modified oligonucleotides further comprise an end block at the 3' end and exhibit exonuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same sequence and number of [~~residues~~] bases.

Claim 36 had been amended as follows:

36. (Twice Amended) The array of claim 34, wherein the modified oligonucleotides further comprise an end block at the 5' end and exhibit exonuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same sequence and number of [~~residues~~] bases.